

PCTWORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : A61K 9/107, 9/51, 47/12, 47/44	A1	(11) International Publication Number: WO 96/24332 (43) International Publication Date: 15 August 1996 (15.08.96)
<p>(21) International Application Number: PCT/US96/01433</p> <p>(22) International Filing Date: 31 January 1996 (31.01.96)</p> <p>(30) Priority Data: 08/384,057 6 February 1995 (06.02.95) US 08/388,088 14 February 1995 (14.02.95) US</p> <p>(71) Applicant: NANOSYSTEMS L.L.C. [US/US]; Building 1, 1250 South Collegeville Road, Collegeville, PA 19426 (US).</p> <p>(72) Inventors: EICKHOFF, W., Mark; 1313 Rhode Island Circle, Downingtown, PA 19355 (US). MUELLER, Karl, R.; 45 Marilyn Avenue, Pexton, PA 19344 (US). ENGERS, David, A.; 480-5 Main Street, Collegeville, PA 19426 (US).</p> <p>(74) Agents: WEST, Paul, B.; Ladas & Parry, 26 West 61st Street, New York, NY 10023 (US) et al.</p>	<p>(81) Designated States: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (KE, LS, MW, SD, SZ, UG), Eurasian patent (AZ, BY, KG, KZ, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).</p> <p>Published <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i></p>	
(54) Title: FORMULATIONS OF COMPOUNDS AS NANOPARTICULATE DISPERSIONS IN DIGESTIBLE OILS OR FATTY ACIDS		
<p>(57) Abstract</p> <p>Nanoparticulate crystalline drug substances formulated in an aqueous phase emulsified in oil, are able to be made at less than 1000 nm size and provide increased bioavailability and lymphatic uptake following oral administration.</p>		

FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

AM	Armenia	GB	United Kingdom	MW	Malawi
AT	Austria	GE	Georgia	MX	Mexico
AU	Australia	GN	Guinea	NE	Niger
BB	Barbados	GR	Greece	NL	Netherlands
BE	Belgium	HU	Hungary	NO	Norway
BF	Burkina Faso	IE	Ireland	NZ	New Zealand
BG	Bulgaria	IT	Italy	PL	Poland
BJ	Benin	JP	Japan	PT	Portugal
BR	Brazil	KE	Kenya	RO	Romania
BY	Belarus	KG	Kyrgyzstan	RU	Russian Federation
CA	Canada	KP	Democratic People's Republic of Korea	SD	Sudan
CF	Central African Republic	KR	Republic of Korea	SE	Sweden
CG	Congo	KZ	Kazakhstan	SG	Singapore
CH	Switzerland	LI	Liechtenstein	SI	Slovenia
CI	Côte d'Ivoire	LK	Sri Lanka	SK	Slovakia
CM	Cameroon	LR	Liberia	SN	Senegal
CN	China	LT	Lithuania	SZ	Swaziland
CS	Czechoslovakia	LU	Luxembourg	TD	Chad
CZ	Czech Republic	LV	Latvia	TG	Togo
DE	Germany	MC	Monaco	TJ	Tajikistan
DK	Denmark	MD	Republic of Moldova	TT	Trinidad and Tobago
EE	Estonia	MG	Madagascar	UA	Ukraine
ES	Spain	ML	Mali	UG	Uganda
FI	Finland	MN	Mongolia	US	United States of America
FR	France	MR	Mauritania	UZ	Uzbekistan
GA	Gabon			VN	Viet Nam

FORMULATIONS OF COMPOUNDS AS NANOPARTICULATE
DISPERSIONS IN DIGESTIBLE OILS OR FATTY ACIDS

5 Field of the Invention

 The present invention relates to formulations of
compounds as nanoparticulate aqueous dispersions
emulsified in digestible oils or fatty acids with or
10 without additional stabilizers. More particularly, the
present invention increases the bioavailability of
pharmacological compounds and allows pharmacological
compounds to be delivered directly to the lymphatic
systems following oral administration.

15

Background of the Invention

 Intestinal lymphatic uptake has long been proposed
as a route for drugs to increase systemic
bioavailability by avoiding first pass metabolism and
20 hepobiliary elimination pathways following oral
administration. However, no strong data in the
literature exists which suggest there is an oral
delivery system which actually can target this
absorption pathway to any great extent. Formulation of
25 drugs in oils and fatty acids is a traditional approach
which has shown some success, but is by no means
predictable. These approaches have focused on
compounds with high log P and high lipid solubility,
and even under these conditions results have been
30 mixed. This approach suffers from the limitation that
most compounds have limited solubility in digestible
oils or fatty acids to the extent that development into
a solid dosage form is not practical, that is, too
large a capsule is needed to provide the dose.

35 Nanoparticles, described in U.S. Patent No.
5,145,684, are particles consisting of a poorly soluble
therapeutic or diagnostic agent onto which are adsorbed

a non-crosslinked surface modifier, and which have an average particle size of less than about 400 nanometers (nm).

5 The present invention provides improved oral bioavailability for any compound which possesses extensive first pass elimination and that can be formulated as a nanoparticulate in a digestible oil or fatty acid. It is theorized that nanoparticles are rapidly carried intact into the intestinal lymphatic
10 ducts/vessels via the lipid transport pathway where subsequent dissolution in lymph/blood partitioning occurs. Eventually, any undissolved nanoparticulate will drain into the systemic circulation and represent a late phase delivery pathway.

15

Summary of the Invention

The present invention provides an orally administratable particle which consists essentially of 0.1-50% by weight of a crystalline drug substance
20 having a solubility in water of less than 10 mg/ml. The drug substance has a non-crosslinked modifier adsorbed on the surface thereof in an amount of 0.1-20% by weight. The particles are suspended in an aqueous phase. The aqueous phase is emulsified in an oil or
25 fatty acid. The particles maintain an effective size of less than 1000 nm.

In a preferred form of the present invention, the oil phase comprises oleic acid.

30

Description of the Preferred Embodiment

The present invention is based on the hypothesis that oral bioavailability can be dramatically improved for any compound which possesses extensive first pass elimination and that can be formulated as a
35 nanoparticulate in a digestible oil or fatty acid.

The present invention can be practiced with a wide variety of crystalline materials that are

water insoluble or poorly soluble in water. As used herein, poorly soluble means that the material has a solubility in aqueous medium of less than about 10 mg/ml, and preferably of less than about 1 mg/ml.

5 Examples of the preferred crystalline material are as follows. The therapeutic candidates include [6-methoxy-4-(1-methylethyl)-3-oxo-1,2-benzisothiazol-2-(3H)-yl] methyl 2,6-dichlorobenzoate, S,S-dioxide, described in U.S. Patent 5,128,339 (WIN 63394),
10 cyclosporin, propanolol, antifungals, antivirals, chemotherapeutics, oligonucleotides, peptides or peptidomimetics and proteins. In addition it is believed that vaccines can also be delivered to the lymphatic system by use of the present invention. The
15 present invention also allows imaging of the intestinal lymphatic system with X-ray or MRI agents formulated as nanoparticles in digestible oils or fatty acids. Potential imaging agents include any X-ray or MRI nanoparticulate core.

20 ~~Suitable surface modifiers can preferably be selected from known organic and inorganic pharmaceutical excipients. Such excipients include various polymers, low molecular weight oligomers, natural products and surfactants. Preferred surface~~
25 ~~modifiers include nonionic and ionic surfactants.~~

Representative examples of surface modifiers include gelatin, casein, lecithin (phosphatides), gum acacia, cholesterol, tragacanth, stearic acid, benzalkonium chloride, calcium stearate, glycerol monostearate,
30 cetostearyl alcohol, cetomacrogol emulsifying wax, sorbitan esters, polyoxyethylene alkyl ethers, e.g., macrogol ethers such as cetomacrogol 1000, polyoxyethylene castor oil derivatives, polyoxyethylene sorbitan fatty acid esters, e.g., the commercially
35 available Tweens, polyethylene glycols, polyoxyethylene stearates, colloidal silicon dioxide, phosphates, sodium dodecylsulfate, carboxymethylcellulose calcium,

carboxymethylcellulose sodium, methylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose phthlate, microcrystalline cellulose, magnesium aluminum silicate, triethanolamine, polyvinyl alcohol, and polyvinylpyrrolidone (PVP). Most of these surface modifiers are known pharmaceutical excipients and are described in detail in the Handbook of Pharmaceutical Excipients, published jointly by the American Pharmaceutical Association and The Pharmaceutical Society of Great Britain, the Pharmaceutical Press, 1986.

Particularly preferred surface modifiers include polyvinylpyrrolidone, tyloxapol, poloxamers such as Pluronic F68 and F108, which are block copolymers of ethylene oxide and propylene oxide, and polyamines such as Tetronic 908 (also known as Poloxamine 908), which is a tetrafunctional block copolymer derived from sequential addition of propylene oxide and ethylene oxide to ethylenediamine, available from BASF, dextran, lecithin, dialkylesters of sodium sulfosuccinic acid, such as Aerosol OT, which is a dioctyl ester of sodium sulfosuccinic acid, available from American Cyanimid, Duponol P, which is a sodium lauryl sulfate, available from DuPont, Triton X-200, which is an alkyl aryl polyether sulfonate, available from Rohm and Haas, Tween 20 and Tween 80, which are polyoxyethylene sorbitan fatty acid esters, available from ICI Specialty Chemicals; Carbowax 3550 and 934, which are polyethylene glycols available from Union Carbide; Crodesta F-110, which is a mixture of sucrose stearate and sucrose distearate, available from Croda Inc., Crodesta SL-40, which is available from Croda, Inc., and SA90HCO, which is C₁₈H₃₇-CH₂(CON(CH₃)CH₂(CHOH)₄CH₂OH)₂. Surface modifiers which have been found to be particularly useful include Tetronic 908, the Tweens, Pluronic F-68 and

polyvinylpyrrolidone. Other useful surface modifiers include:

- decanoyl-N-methylglucamide;
- n-decyl β -D-glucopyranoside;
- 5 n-decyl β -D-maltopyranoside;
- n-dodecyl β -D-glucopyranoside;
- n-dodecyl β -D-maltoside;
- heptanoyl-N-methylglucamide;
- n-heptyl- β -D-glucopyranoside;
- 10 n-heptyl β -D-thioglucoside; n-hexyl β -D-glucopyranoside;
- nonanoyl-N-methylglucamide;
- n-nonyl β -D-glucopyranoside;
- octanoyl-N-methylglucamide;
- 15 n-octyl- β -D-glucopyranoside;
- octyl β -D-thioglucopyranoside; and the like.

Another useful surface modifier is tyloxapol (a nonionic liquid polymer of the alkyl aryl polyether alcohol type; also known as superinone or triton).

20 ~~This surface modifier is commercially available and/or can be prepared by techniques known in the art.~~

Another preferred surface modifier is p-isononylphenoxypoly(glycidol) also known as Olin-10G or Surfactant 10-G, is commercially available as 10G from
25 Olin Chemicals, Stamford, Connecticut.

One preferred surface modifier is a block copolymers linked to at least one anionic group. The polymers contain at least one, and preferably two, three, four or more anionic groups per molecule. Preferred anionic
30 groups include sulfate, sulfonate, phosphonate, phosphate and carboxylate groups. The anionic groups are covalently attached to the nonionic block copolymer. The nonionic sulfated polymeric surfactant has a molecular weight of 1,000-50,000, preferably
35 2,000-40,000 and more preferably 3,000-30,000. In preferred embodiments, the polymer comprises at least about 50%, and more preferably, at least about 60% by

weight of hydrophilic units, e.g., alkylene oxide units. The reason for this is that the presence of a major weight proportion of hydrophilic units confers aqueous solubility to the polymer.

5 A preferred class of block copolymers useful as surface modifiers herein includes sulfated block copolymers of ethylene oxide and propylene oxide. These block copolymers in an unsulfated form are commercially available as Pluronics. Specific examples
10 of the unsulfated block copolymers include F68, F108 and F127.

Another preferred class of block copolymers useful herein include tetrafunctional block copolymers derived from sequential addition of ethylene oxide and
15 propylene oxide to ethylene diamine. These polymers, in an unsulfated form, are commercially available as Tetronics.

The following investigation of preparing nanoparticle dispersions in non-aqueous media was
20 completed for the elastase inhibitor WIN 63394. Oleic acid and three pharmaceutically acceptable oils, soybean oil, corn oil, and safflower seed oil were screened, with and without the addition of secondary stabilizers. Each combination was qualitatively
25 characterized using light microscopy.

Favorable particle size reduction and particle dispersion stability were observed for WIN 63394 nanosuspensions milled with a Pluronic F127 to water ratio of 1:9 in oleic acid. Analysis of dispersions
30 was limited by the their highly viscous nature. Dilution of soybean, corn, and safflower seed oil dispersions stabilized with Pluronic F127 to improve contrast between milled particles and the aqueous and non-aqueous was not effective. A description of the
35 methods and procedures used for media conditioning, product recovery and qualitative microscopic analysis are discussed below.

All experiments requiring milling were completed in a dispersion mill. A 25 ml volume of dispersion was milled using 42.0 g of 0.5 mm acid washed glass beads. At the conclusion of the milling period, vacuum
5 filtration was used to recover the product dispersion.

A Leitz Diaplan microscope with a PL Fluotar 100/1.32 oil object was used to make qualitative observations of the nanoparticle suspension character and estimate particle size of the product dispersions.
10 Particle size distributions could not be quantitatively determined for dispersions in complex media such as oleic acid or oil, using traditional light scattering measurement methods, such as the Microtrac UPA, due to the viscosity and the refractive characteristics of the
15 samples. A Sony color video camera printer was fitted to the microscope and allowed a hard copy micrograph of each sample to be generated for future reference.

The resolution of sample was limited due to the microscope power and the sample character. Dilution of
20 each dispersion was completed using the respective oleic acid or oil medium to improve the contrast between particles and emulsion droplets. Dispersions milled in oleic acid/oil were diluted 1:2 in oleic acid/oil, respectively. This technique increased the
25 resolution of the drug particles for dispersions milled in oleic acid. However, those suspensions milled in oils were unable to be diluted.

Example 1

30 Eight stabilizer systems were screened to identify a potential stabilizer for milling WIN 63394 in oleic acid and was milled four hours. Each nanoparticulate dispersion contained 222.5 mg of WIN 63394 (1%) in a measured amount of stabilizer in 22.25 g oleic acid
35 with 42.0g of 0.5 mm acid washed glass beads. Table I outlines materials and stabilizers used to mill WIN 63394 in oleic acid.

Table I

5

<u>Material</u>	<u>Grade</u>	<u>Source</u>
WIN 63394	-	Sterling- Winthrop
Oleic Acid	NF	Spectrum
<u>Stabilizer</u>		
Tween 80	Reagent	Sigma
SPAN 80	Reagent	ICI
Tyloxapol	Reagent	Sigma
Pluronic F68	NF	BASF
Pluronic F127	NF	BASF
Pluronic L122	NF	BASF
Propylene glycol	Reagent	Aldrich

A description of the trials completed using Example 1 stabilizers and the micrographs for each nanosuspension is found in Table II

10

Table II: Description of WIN 63394 Dispersions Milled
In Oleic Acid

Trial	Stabilizer	Amount (% Total)
1	Tween 80	0.25ml Tween 80 (1.0%)
2	SPAN 80	0.25ml SPAN 80 (1.0%)
3	Tyloxapol	0.25ml Tyloxapol (1.0%)
4	H ₂ O Pluronic F68	1.25ml H ₂ O (5.0%) 250mg F68 (1.0%)
5	H ₂ O Pluronic L122	1.25ml H ₂ O (5.0%) 250mg L122 (1.0%)
6	H ₂ O Pluronic F127	1.25ml H ₂ O (5.0%) 250mg F127 (1.0%)
7	Propylene glycol	6.25ml (25%)
8	50% NaOH solution	12.5ul (0.2%)
9	H ₂ O Pluronic F127	1.25ml H ₂ O (5.0%) 250mg F127 (1.0%)

* - Trial 9 was milled without WIN 63394 as a control
for Trial 6.

In Table II, trials 1-8, WIN 63394 was milled in oleic acid at low solids concentrations. Trial 9 was used as a control for trial 6, which showed favorable particle size reduction of less than 1000 nanometers and good particle dispersion. In trial 8 WIN 63394 was milled without stabilizer for 3 hours and 12.5 µl 50% NaOH solution was added at 3 hours and milled for the final hour.

Good particle size reduction and stability observed in trial 6. That is, 5% H₂O, 1% Pluronic F127 in oleic

acid. In all other trials, 1-5, 7 and 8, agglomeration of drug substance was observed. The stabilizer system of Pluronic F127 in water and oleic acid and increased WIN 63394 concentrations was investigated in Example 2.

5

Example 2

Trials 10-12 were completed using solid stock Pluronic F127. A 10% Pluronic F127 solution was added to trial 13. Trials 14 and 15 were milled in oleic acid as controls for trial 13, trial 14 was milled without WIN 63394 and trial 15 was milled without the addition of Pluronic F127-H₂O stabilizer. A description of the trials completed are found in Table III.

15

Table III: Description of WIN 63394 Dispersions Milled in Oleic Acid at Increased Solids Concentration

Trial	% WIN 63394	Stabilizer (F127:H ₂ O Ratio)	Water	Oleic Acid
10	10.0%	0.75g F127 (dry) (1:5)	15.0%	18.6ml
11	15.0%	0.75g F127 (dry) (1:5)	15.0%	17.5ml
12	20.0%	1.0g F127 (dry) (1:5)	20.0%	15.0ml
13	10.0%	7.5ml-10% F127 soln (1:9)	-	15.0ml
14	-	7.5ml-10% F127 soln (1:9)	-	17.5ml
15	10.0%	-	-	22.5ml

The results of experiments described in Example 2 revealed that at increased solid concentrations, i.e. 20%, dispersion viscosity is increased. As a result, milling efficiency was significantly reduced and the temperature of the suspension during milling increased dramatically. Trial 12 was discontinued after 30 minutes for these reasons. Comparison of Trials 13 and 14 is difficult due to the resolution of the samples. However, minimal agglomeration is observed in Trial 13 when diluted in 2 parts oleic acid. Trial 15 shows significant hard agglomeration in both diluted and undiluted samples.

Example 3

In addition to the dispersions milled in oleic acid, an investigation of soybean, corn, and safflower seed oil was conducted. Again, dispersions were milled using 42g of 0.5 mm acid washed glass beads as the milling agent. Table IV lists the materials used for these oil milling Trials.

Table IV: Materials Used for Screening of Milling Oil Medium

25

<u>Materials</u>	<u>Grade</u>	<u>Source</u>
WIN 63394	-	-
Soybean Oil	Reagent	Sigma
Corn Oil	Reagent	Sigma
Safflower Seed Oil	Reagent	Sigma

30

Based on the favorable results in Trial 6, 5% H₂O-1% Pluronic F127 in oleic acid, 7.5 ml-10% Pluronic F127 solution was added to each oil medium. Controlled dispersions without stabilizer, Trials 16-18, and dispersions with stabilizer and without WIN 63394,

5 trials 20, 22 and 24, were completed to distinguish between drug particles and other components of the emulsion suspension. A description of WIN 63394 dispersions milled in oil mediums with Pluronic F127 is found in Table V.

Table V: Description of WIN 63394 Dispersions Milled in Oil Mediums

10

Trial	Stabilizer	% WIN 63394	Medium/Amount [ml]
16	-	3.0%	Soybean oil/ 24.25ml
17	-	3.0%	Corn oil/ 24.25ml
18	-	3.0%	Safflower seed oil/ 24.25ml
19	7.5ml-10% F127	3.0%	Soybean oil/ 16.75ml
20	7.5ml-10% F127	-	Soybean oil/ 16.75ml
21	7.5ml-10% F127	3.0%	Corn oil/ 16.75ml
22	7.5ml-10% F127	-	Corn oil/ 16.75ml
23	7.5ml-10% F127	3.0%	Safflower seed oil/ 16.75ml
24	7.5ml-10% F127	-	Safflower seed oil/ 16.75ml

Micrographs of the diluted samples from Trials 16-18 showed minimal particle agglomeration. However, as was observed in micrographs of the samples in oleic acid, resolution in between the components in the dispersion was limited. Samples from the trials milled at low solids concentrations, Trials 19, 21 and 23 were observed to have the particles residing within large water droplets. Control Trials 20 and 22 formed stable emulsions while interconnected water droplets were observed in Trial 24. All attempts to dilute the samples in their respective oil medium were unsuccessful.

Example 4

An attempt was made to optimize the Pluronic F127 to water ratio which provides a stable emulsion in oleic acid. The results of this evaluation are described below. Pluronic F127 and water were combined with 10 ml of oleic acid in 20 ml borosilicate glass vials. The vials were placed on a shaker for one hour at 400 rpm at 37 C. Qualitative analysis was completed using photomicroscopy to assess physical stability of each emulsion suspension immediately after shaking and after setting on a bench top for 3 days at 25 °C. The conditions of the trials are listed in Table IV.

Table VI: Description of Pluronic F127/H₂O Optimization Trials

5

Trial	Stabilizer (F127:H ₂ O Ratio)	Water	Oleic Acid
1	1ml-1.0% F127 soln (1:200)	-	10ml
2	1ml-1.0% F127 soln (1:100)	-	10ml
3	1ml-5.0% F127 soln (1:20)	-	10ml
4	1ml-10% F127 soln (1:10)	-	10ml
5	10mg F127 (dry) (1:100)	1ml	10ml
6	50mg F127 (dry) (1:20)	1ml	10ml
7	100mg F127 (dry) (1:10)	1ml	10ml
8	1ml-0.5% F68 soln (1:200)	-	10ml
9	1ml-0.5% F68 soln (1:20)	-	10ml

Trials 1-4 of Example 4 resulted in milky emulsions after shaking. Trials 5-7, which introduced the Pluronic F127 as a dry material also appeared to be well dispersed upon shaking, however the micrographs revealed undissolved F127 material dispersed in the oleic acid. Trials 1-7 separated into 3 phases after 3 days, but were easily returned to a milky emulsion with gentle agitation. Large water droplets were observed in the samples from Trials 8 and 9 after shaking. After 3 days, the emulsion separated into two phases and was difficult to return to an emulsion.

The results of Example 4 demonstrate that it is possible to produce a nanoparticulate aqueous dispersion emulsified in a continuous oil or fatty acid phase. Oleic acid as the fatty acid showed the best results; however, it is anticipated that other fatty acids would also produce stable nanoparticle aqueous dispersion emulsions.

The invention has been described in detail with particular reference to the preferred embodiments thereof, but it will be understood that variations and modifications can be affected within the spirit and scope of the invention.

What is Claimed is:

1. Particles consisting essentially of 0.1-50.0% by weight of a crystalline drug substance having a
5 solubility in water of less than 10.0 mg/ml, said drug substance having a non-crosslinked modifier adsorbed on the surface thereof in an amount of 0.1-20% by weight, said particles suspended in an aqueous phase, the
aqueous phase emulsified in a continuous oil phase,
10 sufficient to maintain an effective particle size of less than 1000 nanometers.

2. The particles according to claim 1 wherein the oil phase comprises oleic acid.

15

3. The particles according to claim 1 wherein the surface modifier comprises poloxamers and water.

4. The particles according to claim 1 wherein the
20 oil phase comprises a fatty acid.

5. The particles according to claim 1 wherein the oil phase comprises a digestible oil.

25 6. The particles according to claim 1 wherein the surface modifier comprises poloxamers 338.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 96/01433

A. CLASSIFICATION OF SUBJECT MATTER

A 61 K 9/107, A 61 K 9/51, A 61 K 47/12, A 61 K 47/44

According to International Patent Classification (IPC) or to both national classification and IPC⁶

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A 61 K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP, A, 0 608 207 (UCB, S.A.) 27 July 1994 (27.07.94), abstract; claims 1,5-8; page 3, lines 31-55; page 4, lines 5-15; examples 1-13. --	1, 3, 5, 6
X	DE, A, 2 714 065 (BOEHRINGER MANNHEIM GMBH) 12 October 1978 (12.10.78), claims 1,2,7-10; page 4, lines 1-9; page 6, lines 1-26; example 2. --	1, 5
X	WO, A, 90/03 164 (PATRALAN LIMITED) - 05 April 1990 (05.04.90), abstract; claims 1,4,7,8,14; examples 1,2,7,10,14,17-22;	1-6



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

Z document member of the same patent family

Date of the actual completion of the international search
03 June 1996

Date of mailing of the international search report

05.07.96

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+ 31-70) 340-2040, Tx. 31 651 epo nl,
Fax (+ 31-70) 340-3016

Authorized officer

MAZZUCCO e.h.

INTERNATIONAL SEARCH REPORT

-2-

International Application No

PCT/US 96/01433

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
	<p>page 20, line 1 in connection with page 21, lines 11-21.</p> <p>--</p>	
Y	<p>EP, A, 0 499 299 (STERLING WINTHROP INC.) 19 August 1992 (19.08.92), claims 1,7,8,11-14; page 2, line 46 - page 3, line 37; page 4, line 13 - page 5, line 25; page 6, lines 19-26.</p> <p>--</p>	1-6
Y	<p>WO, A, 92/06 680 (CORTECS LIMITED) 30 April 1992 (30.04.92), abstract; claims 1,2,9; page 16, lines 13-25,30-32; page 12, line 24 - page 13, line 32.</p> <p>--</p>	1-6
A	<p>EP, A, 0 256 285 (BEHRINGWERKE AG) 24 February 1988 (24.02.88), abstract; claims 1-3; page 1, lines 1-48; page 3, lines 1-5.</p> <p>--</p>	1,3,5, 6
A	<p>EP, A, 0 315 079 (NIPPON SHINYAKU COMPANY) 28 October 1988 (28.10.88), claims 1-7; examples 1,3,6.</p> <p>----</p>	1,5

zum internationalen Recherchen-
bericht über die internationale
Patentanmeldung Nr.

ANNEX

to the International Search
Report to the International Patent
Application No.

ANNEXE

au rapport de recherche inter-
national relatif à la demande de brevet
international n°

La présente annexe indique les membres de la famille de brevets relatifs aux documents de brevets cités dans le rapport de recherche international visé ci-dessus. Les renseignements fournis sont donnés à titre indicatif et n'engagent pas la responsabilité de l'Office.

In Recherchenbericht angeführtes Patentedokument Patent document cited in search report Document de brevet cité dans le rapport de recherche		Datum der Veröffentlichung Publication date Date de publication		Mitglied(er) der Patentfamilie Patent family member(s) Membre(s) de la famille de brevets		Datum der Veröffentlichung Publication date Date de publication	
EP A1	608207	27-07-94		AU	A1	53097784	21-07-94
				CA	AA	21122443	11-07-94
				DE	AA	44011111	01-07-94
				FR	AA	44011111	01-07-94
				GB	AA	44000057	01-07-94
				HU	AA	94000107	01-07-94
				IL	AA	61111111	01-07-94
				NO	AA	44011111	01-07-94
				RU	AA	44011111	01-07-94
				US	A1	61111111	01-07-94
				US	AA	94000107	01-07-94
DE A1	2714065	12-10-78		AT	A	22011778	11-08-80
				AT	B	61111111	01-08-80
				AU	A1	11010101	01-08-80
				CA	B	11010101	01-08-80
				DE	A1	11010101	01-08-80
				FR	A1	11010101	01-08-80
				GB	A1	11010101	01-08-80
				IT	A1	11010101	01-08-80
				JP	B	11010101	01-08-80
				RU	B	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA	11010101	01-08-80
				US	AA		

WO A1 9206680 30-04-92

[illegible][illegible]

EP A1 256285 24-02-88

E
E
A
B
I
N
C
O
A
B
T
A
C
T
E
R
S
P
E
C
I
E
S
L
I
S
T
O
F
T
H
E
U
S
A

7-11-68

[illegible]

EP AC 015075 10-05-89

1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
16
17
18
19
20
21
22
23
24
25
26
27
28
29
30
31
32
33
34
35
36
37
38
39
40
41
42
43
44
45
46
47
48
49
50
51
52
53
54
55
56
57
58
59
60
61
62
63
64
65
66
67
68
69
70
71
72
73
74
75
76
77
78
79
80
81
82
83
84
85
86
87
88
89
90
91
92
93
94
95
96
97
98
99
100
101
102
103
104
105
106
107
108
109
110
111
112
113
114
115
116
117
118
119
120
121
122
123
124
125
126
127
128
129
130
131
132
133
134
135
136
137
138
139
140
141
142
143
144
145
146
147
148
149
150
151
152
153
154
155
156
157
158
159
160
161
162
163
164
165
166
167
168
169
170
171
172
173
174
175
176
177
178
179
180
181
182
183
184
185
186
187
188
189
190
191
192
193
194
195
196
197
198
199
200
201
202
203
204
205
206
207
208
209
210
211
212
213
214
215
216
217
218
219
220
221
222
223
224
225
226
227
228
229
230
231
232
233
234
235
236
237
238
239
240
241
242
243
244
245
246
247
248
249
250
251
252
253
254
255
256
257
258
259
260
261
262
263
264
265
266
267
268
269
270
271
272
273
274
275
276
277
278
279
280
281
282
283
284
285
286
287
288
289
290
291
292
293
294
295
296
297
298
299
300
301
302
303
304
305
306
307
308
309
310
311
312
313
314
315
316
317
318
319
320
321
322
323
324
325
326
327
328
329
330
331
332
333
334
335
336
337
338
339
340
341
342
343
344
345
346
347
348
349
350
351
352
353
354
355
356
357
358
359
360
361
362
363
364
365
366
367
368
369
370
371
372
373
374
375
376
377
378
379
380
381
382
383
384
385
386
387
388
389
390
391
392
393
394
395
396
397
398
399
400
401
402
403
404
405
406
407
408
409
410
411
412
413
414
415
416
417
418
419
420
421
422
423
424
425
426
427
428
429
430
431
432
433
434
435
436
437
438
439
440
441
442
443
444
445
446
447
448
449
450
451
452
453
454
455
456
457
458
459
460
461
462
463
464
465
466
467
468
469
470
471
472
473
474
475
476
477
478
479
480
481
482
483
484
485
486
487
488
489
490
491
492
493
494
495
496
497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525
526
527
528
529
530
531
532
533
534
535
536
537
538
539
540
541
542
543
544
545
546
547
548
549
550
551
552
553
554
555
556
557
558
559
560
561
562
563
564
565
566
567
568
569
570
571
572
573
574
575
576
577
578
579
580
581
582
583
584
585
586
587
588
589
590
591
592
593
594
595
596
597
598
599
600
601
602
603
604
605
606
607
608
609
610
611
612
613
614
615
616
617
618
619
620
621
622
623
624
625
626
627
628
629
630
631
632
633
634
635
636
637
638
639
640
641
642
643
644
645
646
647
648
649
650
651
652
653
654
655
656
657
658
659
660
661
662
663
664
665
666
667
668
669
670
671
672
673
674
675
676
677
678
679
680
681
682
683
684
685
686
687
688
689
690
691
692
693
694
695
696
697
698
699
700
701
702
703
704
705
706
707
708
709
710
711
712
713
714
715
716
717
718
719
720
721
722
723
724
725
726
727
728
729
730
731
732
733
734
735
736
737
738
739
740
741
742
743
744
745
746
747
748
749
750
751
752
753
754
755
756
757
758
759
760
761
762
763
764
765
766
767
768
769
770
771
772
773
774
775
776
777
778
779
780
781
782
783
784
785
786
787
788
789
790
791
792
793
794
795
796
797
798
799
800
801
802
803
804
805
806
807
808
809
810
811
812
813
814
815
816
817
818
819
820
821
822
823
824
825
826
827
828
829
830
831
832
833
834
835
836
837
838
839
840
84

[illegible]

14. Call Center Customer Support
15. Web Application Development
16. Data Analytics and Reporting
17. Cloud Migration Services
18. Mobile App Development
19. Cybersecurity Solutions
20. IT Infrastructure Management
21. Software Integration
22. Network Security
23. Cloud Storage Solutions
24. IT Helpdesk Services
25. System Administration
26. Database Management
27. IT Project Management
28. Hardware Maintenance
29. IT Consulting
30. Network Configuration
31. System Upgrades
32. Data Backup and Recovery
33. IT Compliance
34. Cloud Monitoring
35. IT Training and Certification
36. Network Troubleshooting
37. System Performance Optimization
38. IT Security Audits
39. Cloud Cost Optimization
40. IT Asset Management
41. Network Design
42. System Integration
43. Data Migration
44. IT Support Services
45. Cloud Migration
46. Network Security
47. System Administration
48. Database Management
49. IT Project Management
50. Hardware Maintenance
51. IT Consulting
52. Network Configuration
53. System Upgrades
54. Data Backup and Recovery
55. IT Compliance
56. Cloud Monitoring
57. IT Training and Certification
58. Network Troubleshooting
59. System Performance Optimization
60. IT Security Audits
61. Cloud Cost Optimization
62. IT Asset Management
63. Network Design
64. System Integration
65. Data Migration
66. IT Support Services
67. Cloud Migration
68. Network Security
69. System Administration
70. Database Management
71. IT Project Management
72. Hardware Maintenance
73. IT Consulting
74. Network Configuration
75. System Upgrades
76. Data Backup and Recovery
77. IT Compliance
78. Cloud Monitoring
79. IT Training and Certification
80. Network Troubleshooting
81. System Performance Optimization
82. IT Security Audits
83. Cloud Cost Optimization
84. IT Asset Management
85. Network Design
86. System Integration
87. Data Migration
88. IT Support Services
89. Cloud Migration
90. Network Security
91. System Administration
92. Database Management
93. IT Project Management
94. Hardware Maintenance
95. IT Consulting
96. Network Configuration
97. System Upgrades
98. Data Backup and Recovery
99. IT Compliance
100. Cloud Monitoring
101. IT Training and Certification
102. Network Troubleshooting
103. System Performance Optimization
104. IT Security Audits
105. Cloud Cost Optimization
106. IT Asset Management
107. Network Design
108. System Integration
109. Data Migration
110. IT Support Services
111. Cloud Migration
112. Network Security
113. System Administration
114. Database Management
115. IT Project Management
116. Hardware Maintenance
117. IT Consulting
118. Network Configuration
119. System Upgrades
120. Data Backup and Recovery
121. IT Compliance
122. Cloud Monitoring
123. IT Training and Certification
124. Network Troubleshooting
125. System Performance Optimization
126. IT Security Audits
127. Cloud Cost Optimization
128. IT Asset Management
129. Network Design
130. System Integration
131. Data Migration
132. IT Support Services
133. Cloud Migration
134. Network Security
135. System Administration
136. Database Management
137. IT Project Management
138. Hardware Maintenance
139. IT Consulting
140. Network Configuration
141. System Upgrades
142. Data Backup and Recovery
143. IT Compliance
144. Cloud Monitoring
145. IT Training and Certification
146. Network Troubleshooting
147. System Performance Optimization
148. IT Security Audits
149. Cloud Cost Optimization
150. IT Asset Management
151. Network Design
152. System Integration
153. Data Migration
154. IT Support Services
155. Cloud Migration
156. Network Security
157. System Administration
158. Database Management
159. IT Project Management
160. Hardware Maintenance
161. IT Consulting
162. Network Configuration
163. System Upgrades
164. Data Backup and Recovery
165. IT Compliance
166. Cloud Monitoring
167. IT Training and Certification
168. Network Troubleshooting
169. System Performance Optimization
170. IT Security Audits
171. Cloud Cost Optimization
172. IT Asset Management
173. Network Design
174. System Integration
175. Data Migration
176. IT Support Services
177. Cloud Migration
178. Network Security
179. System Administration
180. Database Management
181. IT Project Management
182. Hardware Maintenance
183. IT Consulting
184. Network Configuration
185. System Upgrades
186. Data Backup and Recovery
187. IT Compliance
188. Cloud Monitoring
189. IT Training and Certification
190. Network Troubleshooting
191. System Performance Optimization
192. IT Security Audits
193. Cloud Cost Optimization
194. IT Asset Management
195. Network Design
196. System Integration
197. Data Migration
198. IT Support Services
199. Cloud Migration
200. Network Security
201. System Administration
202. Database Management
203. IT Project Management
204. Hardware Maintenance
205. IT Consulting
206. Network Configuration
207. System Upgrades
208. Data Backup and Recovery
209. IT Compliance
210. Cloud Monitoring
211. IT Training and Certification
212. Network Troubleshooting
213. System Performance Optimization
214. IT Security Audits
215. Cloud Cost Optimization
216. IT Asset Management
217. Network Design
218. System Integration
219. Data Migration
220. IT Support Services
221. Cloud Migration
222. Network Security
223. System Administration
224. Database Management
225. IT Project Management
226. Hardware Maintenance
227. IT Consulting
228. Network Configuration
229. System Upgrades
230. Data Backup and Recovery
231. IT Compliance
232. Cloud Monitoring
233. IT Training and Certification
234. Network Troubleshooting
235. System Performance Optimization
236. IT Security Audits
237. Cloud Cost Optimization
238. IT Asset Management
239. Network Design
240. System Integration
241. Data Migration
242. IT Support Services
243. Cloud Migration
244. Network Security
245. System Administration
246. Database Management
247. IT Project Management
248. Hardware Maintenance
249. IT Consulting
250. Network Configuration
251. System Upgrades
252. Data Backup and Recovery
253. IT Compliance
254. Cloud Monitoring
255. IT Training and Certification
256. Network Troubleshooting
257. System Performance Optimization
258. IT Security Audits
259. Cloud Cost Optimization
260. IT Asset Management
261. Network Design
262. System Integration
263. Data Migration
264. IT Support Services
265. Cloud Migration
266. Network Security
267. System Administration
268. Database Management
269. IT Project Management
270. Hardware Maintenance
271. IT Consulting
272. Network Configuration
273. System Upgrades
274. Data Backup and Recovery
275. IT Compliance
276. Cloud Monitoring
277. IT Training and Certification
278. Network Troubleshooting
279. System Performance Optimization
280. IT Security Audits
281. Cloud Cost Optimization
282. IT Asset Management
283. Network Design
284. System Integration
285. Data Migration
286. IT Support Services
287. Cloud Migration
288. Network Security
289. System Administration
290. Database Management
291. IT Project Management
292. Hardware Maintenance
293. IT Consulting
294. Network Configuration
295. System Upgrades
296. Data Backup and Recovery
297. IT Compliance
298. Cloud Monitoring
299. IT Training and Certification
300. Network Troubleshooting
301. System Performance Optimization
302. IT Security Audits
303. Cloud Cost Optimization
304. IT Asset Management
305. Network Design
306. System Integration
307. Data Migration
308. IT Support Services
309. Cloud Migration
310. Network Security
311. System Administration
312. Database Management
313. IT Project Management
314. Hardware Maintenance
315. IT Consulting
316. Network Configuration
317. System Upgrades
318. Data Backup and Recovery
319. IT Compliance
320. Cloud Monitoring
321. IT Training and Certification
322. Network Troubleshooting
323. System Performance Optimization
324. IT Security Audits
325. Cloud Cost Optimization
326. IT Asset Management
327. Network Design
328. System Integration
329. Data Migration
330. IT Support Services
331. Cloud Migration
332. Network Security
333. System Administration
334. Database Management
335. IT Project Management
336. Hardware Maintenance
337. IT Consulting
338. Network Configuration
339. System Upgrades
340. Data Backup and Recovery
341. IT Compliance
342. Cloud Monitoring
343. IT Training and Certification
344. Network Troubleshooting
345. System Performance Optimization
346. IT Security Audits
347. Cloud Cost Optimization
348. IT Asset Management
349. Network Design
350. System Integration
351. Data Migration
352. IT Support Services
353. Cloud Migration
354. Network Security
355. System Administration
356. Database Management
357. IT Project Management
358. Hardware Maintenance
359. IT Consulting
360. Network Configuration
361. System Upgrades
362. Data Backup and Recovery
363. IT Compliance
364. Cloud Monitoring
365. IT Training and Certification
366. Network Troubleshooting
367. System Performance Optimization
368. IT Security Audits
369. Cloud Cost Optimization
370. IT Asset Management
371. Network Design
372. System Integration
373. Data Migration
374. IT Support Services
375. Cloud Migration
376. Network Security
377. System Administration
378. Database Management
379. IT Project Management
380. Hardware Maintenance
381. IT Consulting
382. Network Configuration
383. System Upgrades
384. Data Backup and Recovery
385. IT Compliance
386. Cloud Monitoring
387. IT Training and Certification
388. Network Troubleshooting
389. System Performance Optimization
390. IT Security Audits
391. Cloud Cost Optimization
392. IT Asset Management
393. Network Design
394. System Integration
395. Data Migration
396. IT Support Services
397. Cloud Migration
398. Network Security
399. System Administration
400. Database Management
401. IT Project Management
402. Hardware Maintenance
403. IT Consulting
404. Network Configuration
405. System Upgrades
406. Data Backup and Recovery
407. IT Compliance
408. Cloud Monitoring
409. IT Training and Certification
410. Network Troubleshooting
411. System Performance Optimization
412. IT Security Audits
413. Cloud Cost Optimization
414. IT Asset Management
415. Network Design
416. System Integration
417. Data Migration
418. IT Support Services
419. Cloud Migration
420. Network Security
421. System Administration
422. Database Management
423. IT Project Management
424. Hardware Maintenance
425. IT Consulting
426. Network Configuration
427. System Upgrades
428. Data Backup and Recovery
429. IT Compliance
430. Cloud Monitoring
431. IT Training and Certification
432. Network Troubleshooting
433. System Performance Optimization
434. IT Security Audits
435. Cloud Cost Optimization
436. IT Asset Management
437. Network Design
438. System Integration
439. Data Migration
440. IT Support Services
441. Cloud Migration
442. Network Security
443. System Administration
444. Database Management
445. IT Project Management
446. Hardware Maintenance
447. IT Consulting
448. Network Configuration
449. System Upgrades
450. Data Backup and Recovery
451. IT Compliance
452. Cloud Monitoring
453. IT Training and Certification
454. Network Troubleshooting
455. System Performance Optimization
456. IT Security Audits
457. Cloud Cost Optimization
458. IT Asset Management
459. Network Design
460. System Integration
461. Data Migration
462. IT Support Services
463. Cloud Migration
464. Network Security
465. System Administration
466. Database Management
467. IT Project Management
468. Hardware Maintenance
469. IT Consulting
470. Network Configuration
471. System Upgrades
472. Data Backup and Recovery
473. IT Compliance
474. Cloud Monitoring
475. IT Training and Certification
476. Network Troubleshooting
477. System Performance Optimization
478. IT Security Audits
479. Cloud Cost Optimization
480. IT Asset Management
481. Network Design
482. System Integration
483. Data Migration
484. IT Support Services
485. Cloud Migration
486. Network Security
487. System Administration
488. Database Management
489. IT Project Management
490. Hardware Maintenance
491. IT Consulting
492. Network Configuration
493. System Upgrades
494. Data Backup and Recovery
495. IT Compliance
496. Cloud Monitoring
497. IT Training

IT	A	1224586	04-10-90
NL	A	8802659	16-05-89
JF	A2	20000203	05-01-90
JF	B4	7098740	25-10-95
